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Synthesis and antimicrobial activity of some hybrid 2-aryl-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine derivatives

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Some new hybrid 2-aryl-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines have been synthesised which possessed the pyrazole and benzodiazepine heterocycles **2a-t**. Antimicrobial evaluation of the synthesized compounds have been carried out against different strains of bacteria like *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* and fungal strains like *C. albicans*, *A. niger* and *A. clavatus* using serial dilution method. The newly synthesized compounds **2i**, **2j**, **2k**, **2l**, **2m**, **2q** and **2t** have shown significant activity against the above mentioned strains. The reported compounds in the present paper are supported by IR, ¹H and ¹³C NMR, and LC-MS spectral analysis.

Keywords: One-pot synthesis, pyrazole, benzodiazepine, antimicrobial activity

Though many pharmaceutical drugs have been used on bacteria and fungi available in the market, microbial infection is a rising global problem due to the resistance of present antimicrobials^{1,2}. We have observed the increasing level of microbial diseases in the surrounding geographical area too^{3,4}. The only solution is to find new antimicrobials having zero resistance on microbes. Keeping this in mind, we have synthesized a new diverse structure of molecules for fighting against microbial infections based on heterocyclic chemistry. The literature review suggested that heterocyclic compounds have very good pharmacological effects⁵⁻⁸. Recently some review articles were published and on the basis of these articles, it is concluded that pyrazole⁹⁻¹¹ and benzodiazepine¹²⁻¹⁵ showed notable pharmaceutical efficacy and therefore we have selected these versatile motifs in the present work. We have used a hybrid approach, using pyrazole and benzodiazepine in the same structure. Certain commercially available medicines are also having pyrazole and benzodiazepine motif. Some of them are shown in Figure 1 below.

Results and Discussion

Chemistry

The development of non-hazardous synthetic methodologies for organic reactions is one of the most

complicated issues to the organic chemists now a days. In continuation to this, we synthesized 2-aryl-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines (**2a-t**) by a one-pot synthesis with the use of 1-phenyl-3-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)prop-2-en-1-ones (**1a-t**) and benzene-1,2-diamine (Scheme I). This simple reaction was carried out in the presence of catalysts *i.e.* piperidine and acetic acid. 0.01 mol of chalcones (**1a-t**) was added to DMF, after the dissolution of (**1a-t**) benzene-1,2-diamine was added in the double ratio. The reaction was refluxed for 8-10 h for completion.

Antimicrobial Assay

“Antimicrobial activity was accomplished by Mueller Hinton Broth dilution method (Becton Dickinson, USA)¹⁶. The strains were acquired from the IMTECH, Chandigarh, India. Antibacterial activity was screened in triple sets at diverse concentrations of 1000, 500, 250 and 200 µg/mL. The compounds which were found to be active in primary analysis were further diluted and evaluated. 10 µg/mL suspensions were further injected on appropriate media and the growth was noted after one or two days. In antifungal evaluation, primary screening was carried out in six sets at different concentrations of 1000, 500, and 250 µg/mL. The compounds found

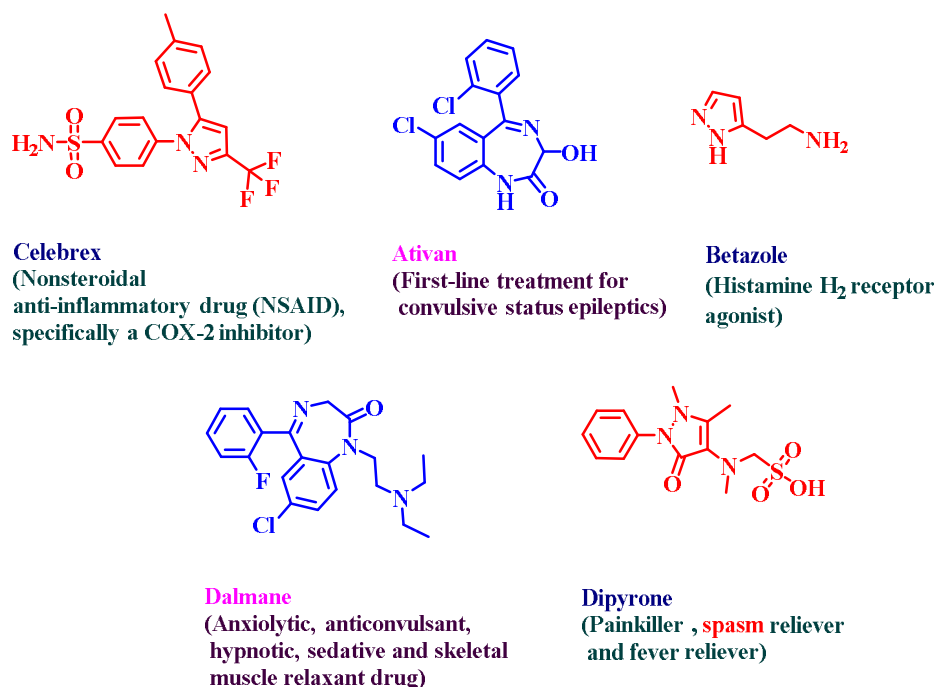
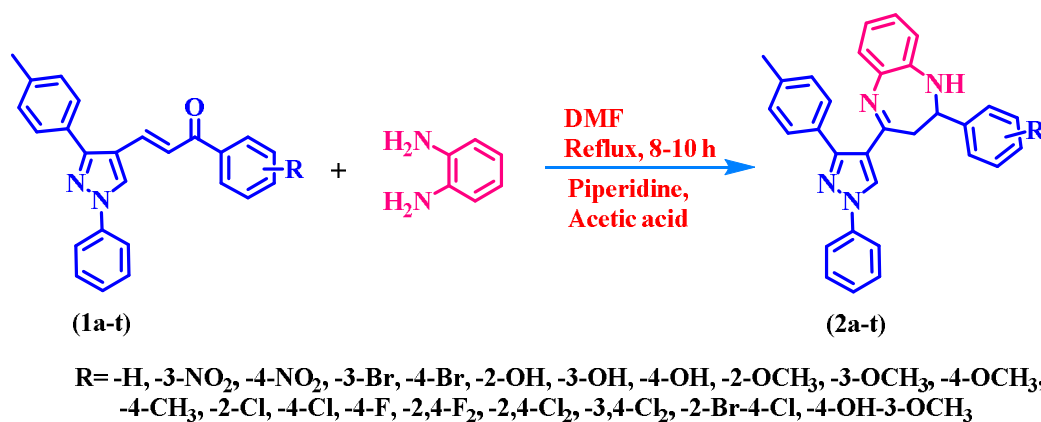


Figure 1 — Commercially available drug candidates containing pyrazole and benzodiazepine

Scheme I — Synthetic pathway of the reported compounds **2a-t**

active were similarly diluted to 200, 125, 100, 62.5, 50, 25, and 12.5 µg/mL concentrations for a secondary screening. Minimum Inhibitory Concentration (MIC) is the lowest concentration which showed no growth of microbes after spot subculture for each compound. In this study, Ciprofloxacin and Nystatin were the standard drugs for evaluating the antibacterial activity and antifungal activity respectively.”¹⁷

Discussion on antimicrobial activity

Antimicrobial activity data are as shown in Table I. A few compounds showed a minimum inhibitory

concentration (MIC) value less than the standard drug, while some compounds showed values comparable to the standard drug. The most active compound among the twenty derivatives is **2q** (-2,4-Cl₂) which showed 12.5 µg/mL MIC value against *E.coli*. Compounds **2m** and **2j** showed significant activity as compared to standard drug (Ciprofloxacin) for *S. aureus* and *S. pyogenes* strains of fungi respectively. Compounds **2l** (-4-CH₃) and **2k** (-4-OCH₃) showed very good activity against *C. albicans*. Compound **2t** (-4-OH-3-OCH₃) showed prominent activity against *A. niger* while compound **2i** exhibited similar potency to standard drug (Nystatin) for *A.*

Table I — Results of biological activities of compounds **2a-t**

Compd	-R	Minimum bactericidal concentrations (MICB) in µg/mL				Minimum fungicidal concentrations (MICF) in µg/mL		
		<i>E. c.</i>	<i>P. a.</i>	<i>S. a.</i>	<i>S. p.</i>	<i>C. a.</i>	<i>A. n.</i>	<i>A. c.</i>
2a	-H	100	125	200	250	250	500	500
2b	-3-NO ₂	125	50	125	200	1000	250	250
2c	-4-NO ₂	62.5	100	125	100	1000	1000	250
2d	-3-Br	100	250	100	100	500	1000	500
2e	-4-Br	250	125	62.5	100	1000	500	250
2f	-2-OH	100	100	100	125	>1000	250	500
2g	-3-OH	250	250	200	250	>1000	>1000	>1000
2h	-4-OH	62.5	100	62.5	100	500	1000	1000
2i	-2-OCH ₃	50	250	100	250	250	100	100
2j	-3-OCH ₃	100	200	62.5	50	100	50	500
2k	-4-OCH ₃	200	250	100	100	50	1000	1000
2l	-4-CH ₃	250	200	62.5	100	25	500	200
2m	-2-Cl	100	100	50	125	250	>1000	1000
2n	-4-Cl	125	62.5	100	200	500	>1000	>1000
2o	-4-F	100	250	125	250	1000	500	1000
2p	-2,4-F ₂	200	250	250	250	>1000	500	>1000
2q	-2,4-Cl ₂	12.5	200	250	100	1000	>1000	>1000
2r	-3,4-Cl ₂	250	100	125	250	500	200	250
2s	-2-Br-4-Cl	62.5	200	200	100	500	250	250
2t	-4-OH-3-OCH ₃	125	100	250	100	1000	25	250
	Ciprofloxacin	25	25	50	50	—	—	—
	Nystatin	—	—	—	—	100	100	100

Escherichia coli (*E.c.*) MTCC-442; *Pseudomonas aeruginosa* (*P.a.*) MTCC-441.

Staphylococcus aureus (*S.a.*) MTCC-96; *Streptococcus pyogenes* (*S.p.*) MTCC-443.

Candida albicans (*C.a.*) MTCC-227; *Aspergillus niger* (*A.n.*) MTCC-282; *Aspergillus clavatus* (*A.c.*) MTCC-1323.

niger and *A. clavatus* strains of fungi. The Standard drug used was Ciprofloxacin and Nystatin for antibacterial and antifungal activity respectively.

Experimental Section

Synthesis of 1-phenyl-3-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one, **1a-t** was achieved by the literature procedure¹⁸.

Synthesis of 2-phenyl-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*benzo[*b*][1,4]diazepines, **2a-t**

Compounds **1a-t** (0.01 mol), benzene-1,2-diamine (0.02 mol) in DMF (10 mL) were taken in a round bottom flask and refluxed for 8-10 h. Piperidine and glacial acetic acid were used as catalysts in the reaction mixture. This reaction mixture was poured into crushed ice to give the product which was filtered and washed with ethyl acetate (to remove any traces of chalcone), followed by hot water (to remove an excess of OPD) and then recrystallization from ethanol (95%).

Physical constants and characterization of 2-phenyl-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*benzo[*b*][1,4]diazepine, **2a:** IR (KBr): 680 (-C-H bending, aromatic ring), 740, 752 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 811 (-C-H bending, 1,4-substituted benzene ring), 962 (-C-H bending, aromatic ring), 1294 (-C-N stretching, pyrazole ring (>N-H)), 1396 (-C-H bending, -CH₃ group), 1474 (-C-H bending, aromatic ring), 1516, 1574 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.52 (dd, *J* = 5.7, 1.9 Hz, 1H, *H*-C-H of benzodiazepine), 2.78 (dd, *J* = 5.7, 2.1 Hz, 1H, *H*-C-H of benzodiazepine), 3.91 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.86-7.67 (m, 18H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.5, 64.4, 112.9, 114.5, 119.7 (2), 121.8, 126.3, 126.7, 126.8, 127.0 (2), 128.2, 128.5 (2), 128.8 (2), 129.4 (2), 129.6 (2), 130.2, 130.5, 131.8, 137.4, 139.8, 140.5, 145.6, 150.2, 162.8; LC-

MS: m/z 454.31 [M^+]. Anal. Calcd for: $C_{31}H_{26}N_4$: C, 81.91; H, 5.77; N, 12.33. Found: C, 81.90; H, 5.75; N, 12.34%.

Physical constants and characterization of 2-(3-nitrophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2b: IR (KBr): 678 (-C-H bending, aromatic ring), 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 825 (-C-H bending, 1,4-substituted benzene ring), 974 (-C-H bending, aromatic ring), 1305 (-C-N stretching, pyrazole ring (>N-H)), 1378 (-C-H bending, -CH₃ group), 1456 (-C-H bending, aromatic ring), 1347, 1512 (-N=O stretching, -NO₂ group), 1524, 1582 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.51 (dd, J = 5.7, 1.1 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.78 (dd, J = 5.3, 1.8 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.93 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.90-8.24 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 39.1, 62.3, 113.2, 114.7, 119.8 (2), 120.4, 121.7, 121.9, 126.2, 126.7, 128.3, 128.6 (2), 129.2, 129.5 (2), 129.6 (2), 130.1, 130.6, 131.6, 133.2, 137.5, 139.9, 144.2, 145.3, 147.5, 150.3, 162.7; LC-MS: m/z 499.59 [M^+]. Anal. Calcd for: $C_{31}H_{25}N_5O_2$: C, 74.53; H, 5.04; N, 14.02. Found: C, 74.55; H, 5.02; N, 14.00%.

Physical constants and characterization of 2-(4-nitrophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2c: IR (KBr): 684 (-C-H bending, aromatic ring), 742, 757 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 816 (-C-H bending, 1,4-substituted benzene ring), 963 (-C-H bending, aromatic ring), 1344 (-C-N stretching, pyrazole ring (>N-H)), 1365 (-C-H bending, -CH₃ group), 1463 (-C-H bending, aromatic ring), 1351, 1537 (-N=O stretching, -NO₂ group), 1526, 1574 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.30 (s, 3H, -CH₃), 2.52 (dd, J = 7.2, 6.0 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.76 (dd, J = 8.3, 7.1 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.90 (s, 1H, -NH of benzodiazepine), 6.84-8.15 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.2, 63.2, 113.3, 114.5, 119.9 (2), 121.6, 123.5 (2), 123.9 (2), 126.3, 126.8, 128.2, 128.5 (2), 129.6 (2), 129.7 (2), 130.2, 130.5, 131.7, 137.4, 139.8, 145.2, 145.8, 146.8, 150.4, 162.6; LC-MS: m/z 499.53 [M^+]. Anal. Calcd for: $C_{31}H_{25}N_5O_2$: C, 74.53;

H, 5.04; N, 14.02. Found: C, 74.54; H, 5.05; N, 14.03%.

Physical constants and characterization of 2-(3-bromophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2d: IR (KBr): 512 (-C-Br stretching, -Br group), 680 (-C-H bending, aromatic ring), 744, 751 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 824 (-C-H bending, 1,4-substituted benzene ring), 971 (-C-H bending, aromatic ring), 1324 (-C-N stretching, pyrazole ring (>N-H)), 1384 (-C-H bending, -CH₃ group), 1470 (-C-H bending, aromatic ring), 1534, 1565 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -CH₃), 2.55 (dd, J = 7.2, 5.9 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.79 (dd, J = 17.0, 2.1 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.94 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.90-7.64 (m, 17H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 39.3, 62.5, 113.1, 114.5, 119.6 (2), 121.5, 122.4, 125.6, 126.3, 126.6, 128.4, 128.7 (2), 129.2, 129.4 (2), 129.7, 129.8 (2), 130.3, 130.7, 131.5, 131.8, 137.6, 139.7, 145.2, 145.4, 150.5, 162.6; LC-MS: m/z 532.14 [M^+]. Anal. Calcd for: $C_{31}H_{25}BrN_4$: C, 69.80; H, 4.72; N, 10.50. Found: C, 69.81; H, 4.70; N, 10.53%.

Physical constants and characterization of 2-(4-bromophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2e: IR (KBr): 543 (-C-Br stretching, -Br group), 692 (-C-H bending, aromatic ring), 742 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 829 (-C-H bending, 1,4-substituted benzene ring), 976 (-C-H bending, aromatic ring), 1286 (-C-N stretching, pyrazole ring (>N-H)), 1372 (-C-H bending, -CH₃ group), 1447 (-C-H bending, aromatic ring), 1512, 1563 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -CH₃), 2.53 (dd, J = 8.8, 2.4 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.74 (dd, J = 9.3, 2.4 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.88 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.88 (m, 17H, Ar-*H*), 8.41 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 39.0, 62.9, 113.3, 114.8, 119.7 (2), 121.3, 121.5, 123.9 (2), 126.3, 126.6, 128.2, 128.5 (2), 129.5 (2), 129.7 (2), 130.2, 130.4, 131.5, 131.7 (2), 137.7, 139.4, 139.8, 145.2, 150.2, 162.6; LC-MS: m/z 532.16 [M^+]. Anal. Calcd for: $C_{31}H_{25}BrN_4$:

C, 69.80; H, 4.72; N, 10.50. Found: C, 69.81; H, 4.71; N, 10.52%.

Physical constants and characterization of 2-(2-hydroxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2f: IR (KBr): 687 (-C-H bending, aromatic ring), 748, 762 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 823 (-C-H bending, 1,4-substituted benzene ring), 982 (-C-H bending, aromatic ring), 1316 (-C-N stretching, pyrazole ring (>N-H)), 1326 (-C-O-H bending, -OH group), 1391 (-C-H bending, -CH₃ group), 1471 (-C-H bending, aromatic ring), 1522, 1535 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.33 (s, 3H, -CH₃), 2.50 (dd, *J* = 8.1, 5.4 Hz, 1H, *H*-C-H of benzodiazepine), 2.76 (dd, *J* = 17.0, 10.1 Hz, 1H, *H*-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.71 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole), 9.66 (s, 1H, -OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 39.4, 56.7, 113.4, 114.6, 115.8, 119.7 (2), 121.4, 121.5, 126.2, 126.3, 126.7, 128.0, 128.4, 128.5 (2), 129.7 (2), 129.8 (2), 130.3, 130.5, 130.7, 131.8, 137.4, 139.7, 145.2, 150.0, 154.2, 162.6; LC-MS: *m/z* 470.25 [M⁺]. Anal. Calcd for: C₃₁H₂₆N₄O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.10; H, 5.56; N, 11.88%.

Physical constants and characterization of 2-(3-hydroxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2g: IR (KBr): 690 (-C-H bending, aromatic ring), 746, 753 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 817 (-C-H bending, 1,4-substituted benzene ring), 959 (-C-H bending, aromatic ring), 1316 (-C-O-H bending, -OH group), 1327 (-C-N stretching, pyrazole ring (>N-H)), 1364 (-C-H bending, -CH₃ group), 1485 (-C-H bending, aromatic ring), 1513, 1575 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.56 (dd, *J* = 5.3, 1.9 Hz, 1H, *H*-C-H of benzodiazepine), 2.78 (dd, *J* = 8.7, 5.7 Hz, 1H, *H*-C-H of benzodiazepine), 3.87 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.80-7.70 (m, 17H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole), 9.24 (s, 1H, -OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 39.4, 63.4, 112.4, 112.8, 113.7, 114.6, 119.4, 119.7 (2), 121.5, 126.3, 126.5, 128.4, 128.7 (2), 129.3 (2), 129.8 (2), 129.9, 130.2, 130.4, 131.8, 137.4, 139.7, 144.8, 145.2, 150.6, 156.6, 162.8; LC-MS: *m/z* 470.24 [M⁺]. Anal. Calcd for:

C₃₁H₂₆N₄O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.13; H, 5.55; N, 11.90%.

Physical constants and characterization of 2-(4-hydroxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2h: IR (KBr): 684 (-C-H bending, aromatic ring), 743, 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 820 (-C-H bending, 1,4-substituted benzene ring), 965 (-C-H bending, aromatic ring), 1332 (-C-O-H bending, -OH group), 1345 (-C-N stretching, pyrazole ring (>N-H)), 1387 (-C-H bending, -CH₃ group), 1473 (-C-H bending, aromatic ring), 1527, 1563 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.55 (dd, *J* = 5.3, 1.9 Hz, 1H, *H*-C-H of benzodiazepine), 2.76 (dd, *J* = 8.7, 5.2 Hz, 1H, *H*-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.68-7.63 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole), 9.08 (s, 1H, -OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 39.3, 63.4, 113.3, 114.6, 115.8 (2), 119.7 (2), 121.5, 126.3, 126.5, 127.2 (2), 128.4, 128.7 (2), 129.4 (2), 129.5 (2), 130.2, 130.7, 131.8, 133.2, 137.4, 139.8, 145.2, 150.1, 156.4, 162.8; LC-MS: *m/z* 470.20 [M⁺]. Anal. Calcd for: C₃₁H₂₆N₄O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.12; H, 5.59; N, 11.90%.

Physical constants and characterization of 2-(2-methoxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2i: IR (KBr): 686 (-C-H bending, aromatic ring), 752, 760 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 814 (-C-H bending, 1,4-substituted benzene ring), 969 (-C-H bending, aromatic ring), 1308 (-C-N stretching, pyrazole ring (>N-H)), 1365 (-C-H bending, -CH₃ group), 1459 (-C-H bending, aromatic ring), 1534, 1574 (-N-H bending, benzodiazepine ring (>N-H)), 2823 (-C-H stretching, -OCH₃ group) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -CH₃), 2.50 (dd, *J* = 5.4, 51.7 Hz, 1H, *H*-C-H of benzodiazepine), 2.78 (dd, *J* = 9.7, 7.6 Hz, 1H, *H*-C-H of benzodiazepine), 3.74 (s, 3H, -OCH₃), 3.89 (s, 1H, -CH of benzodiazepine), 5.85 (s, 1H, -NH of benzodiazepine), 6.87-7.72 (m, 17H, Ar-*H*), 8.41 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.5, 56.2, 57.3, 112.3, 113.4, 114.6, 119.9 (2), 120.7, 121.5, 126.1, 126.3, 126.4, 127.5, 128.6, 128.8 (2), 129.2, 129.4 (2), 129.7 (2), 130.2, 130.7, 131.8, 137.3, 139.6, 145.5, 150.2, 156.4, 162.8;

LC-MS: m/z 484.21 [M^+]. Anal. Calcd for: $C_{32}H_{28}N_4O$: C, 79.31; H, 5.82; N, 11.56. Found: C, 79.30; H, 5.80; N, 11.58%.

Physical constants and characterization of 2-(3-methoxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2j:

IR (KBr): 696 (-C-H bending, aromatic ring), 741, 752 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 825 (-C-H bending, 1,4-substituted benzene ring), 973 (-C-H bending, aromatic ring), 1336 (-C-N stretching, pyrazole ring (>N-H)), 1382 (-C-H bending, -CH₃ group), 1467 (-C-H bending, aromatic ring), 1518, 1553 (-N-H bending, benzodiazepine ring (>N-H)), 2819 (-C-H stretching, -OCH₃ group) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, -CH₃), 2.54 (dd, J = 5.3, 1.8 Hz, 1H, *H*-C-H of benzodiazepine), 2.77 (dd, J = 8.5, 5.2 Hz, 1H, *H*-C-H of benzodiazepine), 3.68 (s, 3H, -OCH₃), 3.92 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.86-7.69 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 39.4, 55.6, 63.3, 112.1, 112.5, 113.1, 114.8, 119.3, 119.9 (2), 121.6, 126.3, 126.8, 128.4, 128.7 (2), 129.6, 129.6 (2), 129.7 (2), 130.0, 130.7, 131.7, 137.6, 140.0, 144.3, 145.4, 150.5, 160.5, 162.8; LC-MS: m/z 484.24 [M^+]. Anal. Calcd for: $C_{32}H_{28}N_4O$: C, 79.31; H, 5.82; N, 11.56. Found: C, 79.33; H, 5.80; N, 11.53%.

Physical constants and characterization of 2-(4-methoxyphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2k:

IR (KBr): 687 (-C-H bending, aromatic ring), 750, 758 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 822 (-C-H bending, 1,4-substituted benzene ring), 964 (-C-H bending, aromatic ring), 1286 (-C-N stretching, pyrazole ring (>N-H)), 1390 (-C-H bending, -CH₃ group), 1474 (-C-H bending, aromatic ring), 1541, 1571 (-N-H bending, benzodiazepine ring (>N-H)), 2831 (-C-H stretching, -OCH₃ group) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.50 (dd, J = 5.4, 1.7 Hz, 1H, *H*-C-H of benzodiazepine), 2.76 (dd, J = 16.9, 10.1 Hz, 1H, *H*-C-H of benzodiazepine), 3.82 (s, 3H, -OCH₃), 3.93 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.63 (m, 17H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 39.4, 55.7, 62.9, 113.4, 114.3 (2), 114.9, 119.6 (2), 121.9, 126.4, 126.6 (2), 126.9,

128.5, 128.8 (2), 129.7 (2), 129.8 (2), 130.3, 130.7, 131.8, 132.8, 137.7, 139.6, 145.5, 150.4, 158.4, 162.6; LC-MS: m/z 484.22 [M^+]. Anal. Calcd for: $C_{32}H_{28}N_4O$: C, 79.31; H, 5.82; N, 11.56. Found: C, 79.29; H, 5.83; N, 11.55%.

Physical constants and characterization of 2-(4-methylphenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2l:

IR (KBr): 674 (-C-H bending, aromatic ring), 747, 759 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 827 (-C-H bending, 1,4-substituted benzene ring), 980 (-C-H bending, aromatic ring), 1314 (-C-N stretching, pyrazole ring (>N-H)), 1328 (-C-H bending, -CH₃ group), 1378 (-C-H bending, -CH₃ group), 1460 (-C-H bending, aromatic ring), 1526, 1579 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.17 (s, 3H, -CH₃), 2.33 (s, 3H, -CH₃), 2.53 (dd, J = 17.0, 2.0 Hz, 1H, *H*-C-H of benzodiazepine), 2.78 (dd, J = 10.1, 2.0 Hz, 1H, *H*-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.90-7.68 (m, 17H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4 (2), 39.3, 63.1, 113.4, 114.5, 119.7 (2), 121.6, 125.6, 126.4, 126.5, 128.2, 128.7 (2), 129.2, 129.6 (2), 129.8 (2), 130.3, 130.5, 131.7, 136.2, 137.4, 137.9, 139.8, 145.2, 150.1, 162.8; LC-MS: m/z 468.20 [M^+]. Anal. Calcd for: $C_{32}H_{28}N_4$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.01; H, 6.03; N, 11.97%.

Physical constants and characterization of 2-(2-chlorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2m:

IR (KBr): 692 (-C-H bending, aromatic ring), 714 (-C-Cl stretching, -Cl group), 742, 762 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 819 (-C-H bending, 1,4-substituted benzene ring), 969 (-C-H bending, aromatic ring), 1306 (-C-N stretching, pyrazole ring (>N-H)), 1369 (-C-H bending, -CH₃ group), 1452 (-C-H bending, aromatic ring), 1537, 1570 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H, -CH₃), 2.50 (dd, J = 8.5, 5.3 Hz, 1H, *H*-C-H of benzodiazepine), 2.74 (dd, J = 5.4, 1.8 Hz, 1H, *H*-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.85-7.64 (m, 17H, Ar-*H*), 8.42 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 38.6, 57.8, 113.3, 114.5, 119.6 (2), 121.8, 126.4, 126.7, 126.9, 127.9, 128.1, 128.2, 128.5 (2), 128.7, 129.7 (2), 129.8 (2), 130.2, 130.5, 131.7,

132.4, 137.4, 140.1, 143.3, 145.4, 150.1, 162.6; LC-MS: m/z 488.20 $[M^+]$. Anal. Calcd for: $C_{31}H_{25}ClN_4$: C, 76.14; H, 5.15; N, 11.46. Found: C, 76.15; H, 5.18; N, 11.45%.

Physical constants and characterization of 2-(4-chlorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2n: IR (KBr): 698 (-C-H bending, aromatic ring), 743, 757 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 778 (-C-Cl stretching, -Cl group), 816 (-C-H bending, 1,4-substituted benzene ring), 972 (-C-H bending, aromatic ring), 1319 (-C-N stretching, pyrazole ring (>N-H)), 1378 (-C-H bending, -CH₃ group), 1475 (-C-H bending, aromatic ring), 1551, 1579 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.52 (dd, J = 9.8, 1.6 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.76 (dd, J = 8.7, 5.3 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.88 (s, 1H, -CH of benzodiazepine), 5.90 (s, 1H, -NH of benzodiazepine), 6.87-7.65 (m, 17H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 39.3, 63.2, 112.8, 114.6, 119.8 (2), 121.6, 123.5 (2), 126.4, 126.8, 128.5, 128.7 (2), 128.9 (2), 129.8 (2), 129.5 (2), 130.2, 130.4, 131.9, 132.4, 137.6, 138.8, 139.9, 145.2, 150.1, 162.6; LC-MS: m/z 488.15 $[M^+]$. Anal. Calcd for: $C_{31}H_{25}ClN_4$: C, 76.14; H, 5.15; N, 11.46. Found: C, 76.15; H, 5.17; N, 11.44%.

Physical constants and characterization of 2-(4-fluorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2o: IR (KBr): 683 (-C-H bending, aromatic ring), 747, 750 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 827 (-C-H bending, 1,4-substituted benzene ring), 975 (-C-H bending, aromatic ring), 1017 (-C-F stretching, -F group), 1328 (-C-N stretching, pyrazole ring (>N-H)), 1358 (-C-H bending, -CH₃ group), 1451 (-C-H bending, aromatic ring), 1536, 1578 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.56 (dd, J = 16.8, 8.2 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.77 (dd, J = 5.4, 1.7 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.91 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.64 (m, 17H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.0, 63.3, 113.3, 114.5, 115.4 (2), 119.8 (2), 121.6, 126.3, 126.6, 128.4, 128.5 (2), 128.7 (2), 129.4 (2), 129.5 (2), 130.2, 130.7, 131.8, 136.4, 137.4, 139.8, 145.1, 150.4, 160.7, 162.5; LC-MS: m/z

472.23 $[M^+]$. Anal. Calcd for: $C_{31}H_{25}FN_4$: C, 78.79; H, 5.33; N, 11.86. Found: C, 78.80; H, 5.35; N, 11.84%.

Physical constants and characterization of 2-(2,4-difluorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2p: IR (KBr): 685 (-C-H bending, aromatic ring), 742, 758 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 815 (-C-H bending, 1,4-substituted benzene ring), 967 (-C-H bending, aromatic ring), 1104 (-C-F stretching, -F group), 1323 (-C-N stretching, pyrazole ring (>N-H)), 1394 (-C-H bending, -CH₃ group), 1484 (-C-H bending, aromatic ring), 1517, 1576 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.55 (dd, J = 10.0, 1.5 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.76 (dd, J = 5.9, 1.7 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.90 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.69-7.62 (m, 16H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.2, 56.3, 104.2, 104.6, 110.7, 113.2, 114.7, 120.1 (2), 121.7, 126.3, 126.7, 128.2, 128.5 (2), 129.4 (2), 129.7 (2), 129.9, 130.2, 130.5, 131.8, 137.4, 139.5, 145.2, 150.2, 159.3, 161.1, 162.7; LC-MS: m/z 490.22 $[M^+]$. Anal. Calcd for: $C_{31}H_{24}F_2N_4$: C, 75.90; H, 4.93; N, 11.42. Found: C, 75.92; H, 4.92; N, 11.42%.

Physical constants and characterization of 2-(2,4-dichlorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2q: IR (KBr): 686 (-C-H bending, aromatic ring), 731 (-C-Cl stretching), 744 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 821 (-C-H bending, 1,4-substituted benzene ring), 956 (-C-H bending, aromatic ring), 1276 (-C-N stretching, pyrazole ring (>N-H)), 1409 (-C-H bending, -CH₃ group), 1452 (-C-H bending, aromatic ring), 1504, 1587 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.33 (s, 3H, -CH₃), 2.52 (dd, J = 5.3, 1.8 Hz, 1H, *H*-C-*H* of benzodiazepine), 2.76 (dd, J = 5.4, 2.9 Hz, 1H, *H*-C-*H* of benzodiazepine), 3.93 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.84-7.66 (m, 16H, Ar-*H*), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 38.4, 57.8, 113.2, 114.7, 119.6, 119.8 (2), 121.7, 126.3, 126.6, 126.9, 128.1, 128.5 (2), 129.4 (2), 129.7 (2), 130.1, 130.4, 131.2, 133.8, 137.4, 139.9, 141.4, 145.2, 150.6, 151.3, 162.8; LC-

MS: m/z 522.15 [M^+]. Anal. Calcd for: $C_{31}H_{24}Cl_2N_4$: C, 71.13; H, 4.62; N, 10.70. Found: C, 71.15; H, 4.63; N, 10.72%.

Physical constants and characterization of 2-(3,4-dichlorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2r: IR (KBr): 690 (-C-H bending, aromatic ring), 727 (-C-Cl stretching), 741, 759 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 824 (-C-H bending, 1,4-substituted benzene ring), 974 (-C-H bending, aromatic ring), 1312 (-C-N stretching, pyrazole ring (>N-H)), 1377 (-C-H bending, -CH₃ group), 1473 (-C-H bending, aromatic ring), 1531, 1565 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H, -CH₃), 2.54 (dd, $J = 8.7, 3.6$ Hz, 1H, *H*-C-*H* of benzodiazepine), 2.77 (dd, $J = 9.3, 5.5$ Hz, 1H, *H*-C-*H* of benzodiazepine), 3.89 (s, 1H, -CH of benzodiazepine), 5.91 (s, 1H, -NH of benzodiazepine), 6.82-7.64 (m, 16H, Ar-*H*), 8.46 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.2, 62.7, 113.3, 114.7, 120.0 (2), 121.8, 125.4, 126.3, 126.7, 128.2, 128.4, 128.6 (2), 129.4 (2), 129.7 (2), 130.2 (2), 130.5, 131.6, 131.8, 131.9, 137.1, 139.4, 143.2, 145.3, 150.2, 162.5; LC-MS: m/z 522.12 [M^+]. Anal. Calcd for: $C_{31}H_{24}Cl_2N_4$: C, 71.13; H, 4.62; N, 10.70. Found: C, 71.12; H, 4.65; N, 10.69%.

Physical constants and characterization of 2-(2-bromo,4-chlorophenyl)-4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine, 2s: IR (KBr): 513 (-C-Br stretching, -Br group), 682 (-C-H bending, aromatic ring), 719 (-C-Cl stretching), 740, 756 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 818 (-C-H bending, 1,4-substituted benzene ring), 965 (-C-H bending, aromatic ring), 1342 (-C-N stretching, pyrazole ring (>N-H)), 1386 (-C-H bending, -CH₃ group), 1482 (-C-H bending, aromatic ring), 1520, 1573 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.52 (dd, $J = 9.3, 5.5$ Hz, 1H, *H*-C-*H* of benzodiazepine), 2.78 (dd, $J = 5.7, 2.1$ Hz, 1H, *H*-C-*H* of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.87-7.68 (m, 16H, Ar-*H*), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 38.4, 59.3, 113.1, 114.9, 120.1 (2), 121.7, 123.4, 126.5, 126.8, 128.1, 128.3 (2), 129.5 (2), 129.6 (2), 129.9, 130.2, 130.4, 130.7, 131.8, 133.0, 137.4, 139.5,

143.7, 145.2, 150.6, 162.7; LC-MS: m/z 566.11 [M^+]. Anal. Calcd for: $C_{31}H_{24}BrClN_4$: C, 65.56; H, 4.26; N, 9.87. Found: C, 65.55; H, 4.27; N, 9.86%.

Physical constants and characterization of 2-methoxy-4-(4-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-yl)phenol, 2t: IR (KBr): 688 (-C-H bending, aromatic ring), 744, 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 821 (-C-H bending, 1,4-substituted benzene ring), 950 (-C-H bending, aromatic ring), 1060, 1220 (-C-O-C stretching, -OCH₃ group), 1276 (-C-N stretching, pyrazole ring (>N-H)), 1386 (-C-O-H bending, -OH group), 1409 (-C-H bending, -CH₃ group), 1456 (-C-H bending, aromatic ring), 1506, 1589 (-N-H bending, benzodiazepine ring (>N-H)) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H, -CH₃), 2.53 (dd, $J = 7.2, 6.0$ Hz, 1H, *H*-C-*H* of benzodiazepine), 2.75 (dd, $J = 8.8, 3.4$ Hz, 1H, *H*-C-*H* of benzodiazepine), 3.74 (s, 3H, -OCH₃), 3.90 (s, 1H, -CH of benzodiazepine), 5.87 (s, 1H, -NH of benzodiazepine), 6.70-7.67 (m, 16H, Ar-*H*), 8.47 (s, 1H, -CH of pyrazole), 9.98 (s, 1H, -OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 38.7, 56.4, 63.5, 110.3, 113.4, 114.7, 115.2, 119.2, 119.7 (2), 121.7, 126.3, 126.8, 128.2, 128.5 (2), 129.4 (2), 129.8 (2), 130.1, 130.4, 131.5, 137.2, 139.9, 145.3, 146.8, 147.5, 150.2, 162.7; LC-MS: m/z 500.23 [M^+]. Anal. Calcd for: $C_{32}H_{28}N_4O_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.66; N, 11.20%.

Conclusion

In conclusion, new hybrids of pyrazole and benzodiazepine have been synthesized and characterized by different spectral techniques. All newly synthesized compounds were evaluated for their antibacterial and antifungal activity against different strains of bacteria and fungi using serial dilution method. On the basis of above mentioned data of biological activity, it may be concluded that synthesized novel series of compounds exhibited good to excellent activity against bacterial and fungal strains. Evaluation of compounds **2j**, **2m** and **2q** exhibited excellent activity against bacterial strains while compounds **2i**, **2k**, **2l** and **2t** showed prominent activity against fungal strains. Results of biological activity conclude that electron withdrawing and electron donating groups were much effective for bacterial and fungal strains respectively.

Supplementary Information

Supplementary information is available in the website <http://nopr.niscair.res.in/handle/123456789/60>.

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